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Application for Research Grant
(Use extra pages as needed)

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Date: May 25, 1973

1. Principal Investigator (give title and degrees):
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2. Institution & address:
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3. Department(s) where research will be done or collaboration provided:
Pathology and Medical Research, St. Margaret's Hospital

4. Short title of study:
The interaction of smoke, alcoholism and malnutrition on phagocytic function

5. Proposed starting date: January 1, 1974

6. Estimated time to complete: 3 years

7. Brief description of specific research aims:

The studies to be carried out in this project will utilize alveolar macrophages and peripheral blood leukocytes isolated from smokers, alcoholics, undernourished patients, various combinations of these criteria and appropriate control subjects. The effect of in vitro addition of whole smoke, gas phase and water soluble phase, will also be investigated. Where pertinent, assays will also be conducted during or immediately following phagocytosis.

The experiments may be divided into three major catagories: (1) energy production and uptake of particles; (2) metabolic activities involved in the production and utilization of microbicidal agents; and (3) microbicidal activities.

1. Metabolic activities involved in energy production and uptake of particles.

a. Glycolytic activity as measured by lactate production from both endogeneous substrates and added glucose; glycogen content of the phagocytes.

b. Tricarboxylic acid cycle activity as measured by $^{14}CO_2$ production from glucose-6-^{14}C and succinate 1-4-^{14}C; respiratory activity of intact cells; oxidative phosphorylation by macrophage mitochondria as measured by P/O ratios with succinate and alpha-ketoglutarate as substrates.

c. Lipid synthesis and turnover as measured by acetate-1-^{14}C and ^{32}P incorporation in both whole cells and membrane fractions.

d. Phagocytic activity of intact cells with viable and heat killed bacteria and inert particles as measured by light microscopy.

2. Metabolic activities involved in microbicidal properties.

a. Hexose monophosphate shunt (HMS) activity as measured by glucose-1-^{14}C and glucose-6-^{14}C oxidation and glucose utilization; glucose-6-phosphate and 6-phosphogluconate dehydrogenase activities.

b. NADPH, NADH, L- and D-amino acid oxidase activities of phagocytes suspended in glycerin; H_2O_2 production and formate 1-^{14}C oxidation.

c. Peroxidase activities of cell homogenates and subcellular fractions as measured by guaiacol oxidation, amino acid decarboxylation and iodination of bacteria; catalase activity of homogenates and subcellular fractions.

d. Lysosomal enzyme activities, i.e. phosphatases, proteases, nucleotidase, DNAase, RNAase, beta-glucoronidase and lysozyme.

3. Microbicidal activity.

a. Antimicrobial activities of intact phagocytes against gram positive and gram negative bacteria, viruses and fungi in presence and absence of serum.

b. Antimicrobial activities of subcellular fractions in correlation with peroxidase activities as measured by amino acid decarboxylation and iodination.

8. Brief abstract of working hypothesis:

This project is concerned with a systematic exploration of the total phagocytic process in alveolar macrophages and peripheral blood leukocytes collected from smokers, alcoholics and undernourished patients. Hopefully, the information derived from this study will establish what specific mechanism(s), if at all, are responsible for the increased susceptibility to infection commonly observed in these patients. Emphasis will be placed on the possible interaction of smoking, alcoholism and undernourishment on the overall host defense mechanisms of man. The study will include uptake of viable bacteria and inert particles, investigation of the various metabolic activities that are involved and influenced by the phagocytic process and a critical evaluation of the different bactericidal mechanisms that operate in the whole cell and different subcellular fractions.

Within the past decade considerable advances have been made in our knowledge and methodology of the total phagocytic activity of leukocytes. For example, this laboratory and others have demonstrated that particle uptake is an active process requiring glycolytic activity in polymorphonuclear neutrophils and oxidative energy in alveolar macrophages. However, inactivation of bacteria appears chiefly to be

related to the phagocytosis associated oxidative events. For example, phagocytosis stimulates production of H_2O_2 and increases peroxidase activity. These reactants couple with a halide to form a potent antimicrobial system.

Knowledge such as this may now permit us to study systematically the total phagocytic process in the smokers with and without the additional stress of alcoholism and/or undernourishment from a vantage point heretofore not possible. Hopefully the knowledge to be gained from this investigation will have immediate practical application.

a. Smoking and host defense. It is generally held that smokers are especially susceptible to respiratoryinfections (1-5). However, contrary evidence has been frequently reported. For instance, Boake (6) found no differences due to smoking habits in respiratory illness in a study of 59 different families. Dowling et al (7) observed no statistical differences due to smoking in a double blind study where they exposed 328 non-smokers and 249 smokers to "infectious cold agent" and 111 non-smokers and 78 smokers to placebo. Brown and Campbell (8) reported that tuberculosis is associated more with drinking habits rather than with smoking habits. In a study of 100 patients, Potter et al (9) concluded that the normal bronchial clearance mechanism is able to prevent colonization of pathogenic bacteria and this ability is not impaired in smokers. Post-operative pulmonary complications were reported to be high in smokers (10); although Wiklander and Norlin (11) found no evidence to support such a hypothesis in 200 patients undergoing operations in winter months. Presumably other factors such as alcoholism and undernutrition rather than smoking are involved in the higher incidence of respiratory diseases in smokers. Controlled studies and specific in vitro examination of the recently described mechanisms of the phagocytes should be fruitful in the elucidation of the possible potentiating effects of other stress factors.

Many reports have appeared in the literature regarding the effect of smoke on the pulmonary clearance of both inert particles and viable bacteria. Necessarily most of these studies were in experimental animals and generally showed an impaired function in vitro. Studies on living animals are, however, equivocal. Albert et al (12) and Holma (13) found decreased clearance on acute smoke exposure, whereas LaBelle et al (14) found no ill effects of smoke on pulmonary clearance. Human tracheal and lung clearance in smokers is reported to be normal by Luchsinger et al (15); Albert et al (16) reported, however, that 8 out of 14 smokers demonstrated decreased clearance rates. Nutritional status and drinking habits of these subjects were not reported. In a study of life time elderly smokers and non-smokers, Paiva et al (17, 18) found that neither percent clearance nor half-time of clearance are altered due to smoking. Multiple regression analysis for different variables such as sex, age, height, smoking, forced expiratory volume vital capacity and flow rate indicated that only age alters clearance rates at a statistical significance of around 10%. Besides these conflicting reports, it should be emphasized that pulmonary clearance kinetics by itself may not be a good index of pulmonary defense capacity. Green and Kass (19) in an elegant study using ^{32}P labelled Staphylococcus aureus or

Proteus mirabilis have demonstrated that pulmonary clearance of bacteria and bactericidal activity do not parallel each other. In vitro investigations with isolated phagocytes and with the newly available methodology may prove to be a fruitful approach in the resolving of these apparent paradoxes.

The effect of smoking on particle uptake and bactericidal activity of alveolar macrophages has received considerable attention in the past few decades. Most of these investigations indicate that alveolar macrophages isolated from either smokers or animals exposed to smoke show no alteration in their ability to ingest particles; phagocytic activity is also not altered on addition of smoke in vitro. However, bactericidal activity appears to be decreased under these conditions (20-24). Also, LaBelle et al (25,14) found that phagocytosis was not affected on exposing rats to cigarette smoke. It is well established now that particle uptake and bactericidal activity depend upon different metabolic activities of the phagocyte. Since smoke appears to decrease bactericidal activity without altering uptake, an investigation of the effect of smoke on the various metabolic activities of the phagocyte should increase our understanding of possible ill effects of smoke on pulmonary defense mechanisms. Further, a complete understanding of any ill effects of smoke may pave the way for possible corrective measures.

Smoking appears to have toxic effects on phagocytes other than alveolar macrophages. Thus, Eichel and Shahrik (26) have shown that the respiratory and glycolytic activities of oral leukocytes are considerably decreased following smoking. Since, at least some of the toxic agents in smoke are soluble in water (20,27) and nicotine alters the respiratory activity of alveolar macrophages (28), it is possible that the effects of smoke might be reflected by all the phagocytes of the host including the peripheral blood leukocytes. Since these cells are easily obtained and constitute a well defined model of one of the major host defense system, a systematic investigation of these systems will be of considerable interest.

Some investigators have examined the effects of smoke and its constitutents on phagocytes at the molecular level. Thus, Kyle and Riesen (29) have shown that lung mitochondria looses oxidative phosphorylation efficiency on smoking. A general disruption of internal mitochondrial structure has also been reported (30). Nicotine has been demonstrated to decrease ATPase activity of sheep alveolar macrophages (28). Powell and Green (31) have reported that smoke decreases 3-phosphoglyceraldehyde dehydrogenase activity of rabbit alveolar macrophages but did not affect glucose-6-phosphate and lactate dehydrogenases. A decrease in oxido-reductases in biopsy material from smokers by histochemical techniques has also been reported (32). In spite of these numerous studies, proper emphasis on the metabolic and enzymatic activities of these phagocytes that are directly involved in particle uptake and microbicidal function is still lacking. Also, these investigations should be carried out when the phagocytes are actively involved in the performance of their physiological function, i.e. during engulfment, so that a proper understanding of the correlation of the metabolic activities and susceptibility to infection might result.

b. Alcoholism and host defense. In most of the studies on the effect of smoke on the host defense mechanism, sufficient attention has not been paid to the possibility of other stress factors that might be acting independently or synergistically to decrease resistance to infection. There is some preliminary evidence in the literature to indicate that other stress factors may indeed play a major role in the increased susceptibility to infection commonly attributed to smoking. For instance, although smokers are generally considered to be more susceptible to tuberculosis, alcohol consumption has also been suspected as a factor in the etiology of tuberculosis; however, the evidence for the involvement of alcoholism has been inconclusive (33). As early as 1924, Stillman (34) reported the persistance of inspired bacteria in lungs of mice which received alcohol. In a more recent investigation of this problem, Brown and Campbell (8) have concluded that alcohol and not smoking was more directly associated with tuberculosis. Pulmonary clearance of viable bacteria has been shown to be decreased by ethanol intake (35). This effect was found to be dose related and was unrelated to ethanol induced respiratory depression. Alcohol has also been shown to have a migration inhibitory effect on alveolar macrophages (36), peritoneal leukocytes (37,38) and peripheral blood leukocytes (39). Phagocytosis is also reported to be decreased following alcohol intake (37,38).

The mechanism by which ethanol interfers with phagocytic function is not known. Numerous clinical reports of post alcoholic hypoglycemia have appeared in the literature. Also, liver biopsies of alcoholic patients have revealed that glycogen content is low or completely absent (40-43). In animals decreased hepatic glycogen levels after ethanol infusion even with normal blood glucose levels have also been reported (44). It is possible that leukocyte glycogen levels also decrease due to alcoholism. Since leukocytes derive their energy for phagocytosis from their glycogen stores and blood glucose, the possible malfunction of leukocytes in alcoholism might be due to a lack of energy production. Alcohol may also interfere in the functions of the phagocyte through the induction of the microsomal ethanol oxidizing system (45). NADPH oxidase is a vital component in the microbicidal system providing H_2O_2 for the peroxidase-H_2O_2-halide system. Since the microsomal ethanol oxidizing system competes with NADPH oxidase for NADPH, low H_2O_2 production leading to decreased bactericidal activity might result. It is obvious from the above that the possible interaction of alcoholism with smoking needs careful investigation.

c. Malnutrition and host defense. Another possible stress factor that affects host defense mechanisms and may play a major role in the increased susceptibility to infection observed in smokers is malnutrition. Green and Kass (35) have demonstrated that acute starvation decreases pulmonary clearance significantly. Protein deficiency is known to decrease phagocytic activity of blood leukocytes (46) and peritoneal macrophages (47). Morbidity rates in iron deficiency (48) and urinary tract infections in anemia (49) are reported higher than in normal. Both thiamine and riboflavin deficiencies in rats and mice result in increased fatality rates following infection with Diplococcus pneumoniae (50-52). Folic acid deficient guinea pigs are also more susceptible to infections (53). Respiratory, genito-urinary and other

infections are reported by many workers to be more frequent, persistent and often fatal in vitamin A deficient subjects (54-59). Leukocytes from animals fed diets that are low in protein and vitamins exhibit depressed phagocytic activity (60). Recently we have demonstrated a markedly decreased bactericidal activity and a considerably low phagocytic stimulation of hexose monophosphate shunt activity in leukocytes isolated from children suffering from severe malnutrition (61). The major biochemical defect in these phagocytes appears to be a low NADPH oxidase which also fails to respond with the normal stimulation observed in control subjects during phagocytosis (62). Since smoking suppresses appeptite and smokers generally have a history of poor dietary habits, the contribution of the nutritional status of the smoker to the reported increased susceptibility to infection may be pertinent.

The interaction between smoking, alcoholism and undernutrition is complex. Alcoholics aregenerally undernourished because of their altered pattern of food intake caused by the high calorie contribution of alcohol intake without providing the essential nutrients. Also, recent evidences indicate that ethanol decreases the absorption of essential nutrients such as folic acid (63), thiamine (64), vitamin B_{12} (65) and amino acids (66-68). In addition, alcohol may also increase the requirements of vital nutrients; for instance, extra folate is reported to be required by the alcoholic for normal bone marrow function (69). Thus, alcoholism by direct and indirect mechanisms aggravates undernutrition. Undernutrition also interfers with alcohol metabolism causing a viscious cycle to operate. For instance, half-life of blood alcohol after ingestion in rats is markedly prolonged in protein deficiency. Since both undernutrition and alcoholism adversely affect host defense mechanisms and a high percent of the smoking population is also alcoholic and hence undernourished, the general concept that smokers are more susceptible to infection needs a critical re-evaluation.

9. Details of experimental design and procedures.

a. Description of groups to be studied.

(1). Smokers, ex-smokers and non-smokers: Our patient population consisting of smokers will be derived mainly from the Veterans Administration and Boston City Hospitals in Boston. The degree of smoking will be evaluated by questionnaire method. It is anticipated that an ample supply of patients will be available. Groups will be made from 8-10 patients undergoing bronchoscopy per week. It is expected that some of these patients will have pulmonary infection. Where posssible these patientswill be examined before, during and after treatment.

(2). Alcoholics: Chronic alcoholics will consist of patients recuperating at Boston City and Veterans Administration Hospitals with and without cirrhosis of the liver and the following: iron deficiency anemia; folate deficiency anemia; iron and folate deficiency anemia. Patients with any superimposed infections will also be studied. Acute alcoholics (recent drinking) with and without infections will be

patients who arrive at the Alcoholic Clinic of Boston City and Veterans Administration Hospitals inebriated within the last 24 hours; they usually are admitted in a state of intoxication. They are automatically hospitalized for nine days, after which they may be discharged or admitted to the medical ward for further study, if further medical attention is indicated. These patterns are referred to the Clinic by social agencies. There is no limit as to the number of alcoholic patients available. All patients will be studied within one week of their admisstion and studies repeated prior to discharge (except for cirrhosis, patients are discharged well and without anemia). Appropriate and comparable (i.e. sex, age, socio-economic status) controls will be similarly studied.

(3). Undernourished: Undernourished subjects for this study will be derived mainly from the out-patient clinics of St. Margaret's Hospital, Boston, Veterans Administration Hospital, Boston and Boston City Hospital, Boston. Pregnant women with anemia which is primarily nutritional in origin are readily available at St. Margaret's Hospital for study. Patients who appear to be undernourished and come to the outpatient clinics of Veterans Administration and Boston City Hospitals with minor illnesses will be referred to the laboratory. Social agencies will also be referring undernourished people to these hospitals. Some of these subjects will also be smokers. Phagocytes will be isolated from these subjects for study and where possible they will be followed after rehabilitation.

Approximately 8 to 10 patients per week are bronchoscoped and will be available for this study. Dr. Joseph Vitale will coordinate in this aspect. It is expected that this population of patients will permit us to develop groups as indicated in the table below. Both alveolar macrophages and peripheral leukocytes when desired will be obtained.

The classification of the various groups to be studied is shown in the table below.

GROUPS OF SUBJECTS FOR INVESTIGATION

Group	Smoking	Poor nutritional status	Alcoholism
1	-	-	-
2	-	-	+
3	-	+	-
4	-	+	+
5	+	-	-
6	+	-	+
7	+	+	-
8	+	+	+

- absent
+ present

b. Evaluation of nutritional status. On each group the following, where appropriate, will be determined using conventional or micro techniques. Anthropometric measurements, especially height, weight and skin fold thickness, will be obtained and related to normal values recommended by the World Health Organization. A dietary survey by questionnaire method will be conducted to assess the history of previous food intake. Where feasible (especially in hospitalized subjects), food intake will be measured to evaluate the effect of treatment. Biochemical assessment will be used to specify the nutritional deficiency encountered. Blood analysis will include hemoglobin, hematocrit, peripheral blood differentials and PMN lobe counts. Serum analysis will be used to estimate iron, total iron binding capacity, folate (both N5-methyl-tetrahydrofolate and tetrahydrofolate), vitamin A, proteins by electrophoresis and pertinent serum enzymes. Alcohol acetaldehydes and triglycerides will also be estimated in alcoholic subjects. Erythrocyte transketolase and GSSG reductase will be estimated to assess thiamine and riboflavin nutritional status. Urine will be examined for albumin and bacteriuria. Standard liver function tests will also be conducted and where possible light and electron microscopic evaluation of liver morphology will be done from biopsy material.

c. Evaluation of host defense mechanisms.

(1). Isolation of phagocytes: Leukocytes will be isolated aseptically from peripheral blood by the dextran flotation technique (70). Blood will be drawn into a syringe containing 0.5 ml of 20% dextran and 200 units of heparin per 10 ml of blood. The blood, heparin and dextran suspensions will be mixed, all bubbles expelled and the syringe permitted to stand in an inverted position at room temperature for 30 to 45 minutes. The resulting buffy coat leukocytes will be expelled through a bent needle and washed twice in buffer medium, centrifuged at 200 g for 5 minutes and made up to the desired volume with buffered medium. Total and differential leukocyte counts will be made from both the peripheral blood and isolated suspensions by conventional techniques. The resulting cells will be used in experiments described below.

Alveolar macrophages will be isolated essentially by the method of Finley et al (71). Briefly, using topical xylocaine anesthesia, the trachea will be intubated with a size 19 Metras bronchographic catheter under fluoroscopic control. By inflating the later cuff at the catheter tip, a portion of the lower lobe will be isolated and lavaged with four to five 50 ml aliquots of normal saline. The lavage fluid will be centrifuged twice at 250 g for 10 minutes. The isolated macrophages will be brought up to the desired concentration and used for the different studies.

(2). Cell homogenate preparation: Cells to be homogenized are suspended in 0.25 M sucrose. They are homogenized for 2 minutes at 3800 rpm in a glass Potter-Elvejhem homogenizer with a motor driven teflon tipped pestle. Homogenization and centrifugation is done at 4°C in a Servall RC-2 centrifuge. The uncentrifuged homogenate, the 20,000 g 30 minute pellet fraction (lysosomes) and the 20,000 g 30 minute supernatant fluid fraction are to be studied for bactericidal and metabolic activities.

Mitochrondria from alveolar macrophages will be prepared by conventional techniques. Macrophages are homogenized in 0.25 M sucrose containing 0.07 M mannitol and 0.02 M ethylenediaminetetra acetic acid (pH 7.4) and centrifuged at 600 g for 10 minutes to remove nuclei and unbroken cells. The pellet is rehomogenized and recentrifuged at 600 g for 10 minutes. The combined supernatants are then centrifuged twice at 17,000 g for 20 minutes. The mitochrondrial pellet is resuspended in 0.25 M sucrose containing 0.07 M mannitol and 0.1 mM MgC_{12} and 0.01 M phosphate buffer, pH 7.4

(3). Effect of smoke in vitro: Smoke for in vitro studies will be drawn from both filter and non-filter types of cigarettes in a 50 ml syringe modified to accept a cigarette. A measured volume of the smoke from the second syringe-fill, either before or after filtration through buffer at pH 7.4, will be introduced into the reaction vessel covered with a rubber cap. When necessary the effect of water soluble agents will also be investigated.

(4). Procedures for studies of metabolic activities: Lactate estimations will be done by the colorimetric method of Barker and Sumerson (72). Glucose utilization will be measured by utilizing glucose oxidase (73). Glycogen will be estimated as glucose equivalents by glucose oxidase following hydrolysis. Radioactive CO_2 production from labelled substrates will be absorbed in 20% KOH contained in the center wells of Warburg flasks and counted in Bray's solution in a Packard Tricarb liquid scintillation spectrophotometer. Oxygen consumption will be measured either in a Warburg apparatus or with an oxygen electrode. Oxidative phosphorylation at site 2 will be assayed by the method of Lee et al (74). For phosphorylation at site 3, succinate or alpha-ketoglutarate will be replaced by 0.5 M ascorbate N, N, N', N'-tetramethylphenylenediamine (0.3 M) and 0.1 μg/ml antimycin A_1. Acetate ^{14}C and ^{32}P incorporation into whole cells and into membrane fractions will be studied as described in our previous publication (75). As necessary, the lipid fractions will be separated and quantitated by thin layer chromatography or by gas liquid chromatography.

Hexose monophosphate shunt activity will be calculated from glucose utilization and glucose-1-^{14}C and glucose-6-^{14}C oxidation by the method of Katz and Wood (76). Glycerinated phagocytes are prepared for enzyme assays by adding 0.6 ml of cell suspension to 1.4 ml of 95% glycerin. Glucose-6-phosphate dehydrogenase will be assayed by measuring $NADP^+$ reduction at 340 nm in a medium containing 200 μmoles of Tris (pH 7.5), 10 μmoles of $MgCl_2$, 0.625 μmole of $NADP^+$ and 5 μmoles of glucose-6-phosphate in 3 ml. 6-phosphogluconate dehydrogenase will be assayed in a similar reaction mixture were glucose-6-phosphate is replaced with 10 μmoles of 6-phosphogluconate. NADPH oxidase will be assayed by measuring the oxidation of NADPH at 340 nm in a reaction mixture containing 300 μmoles of phosphate buffer at pH 5.5, 1.0 μmole of MnC_{12}, 200 μmoles of ethanol and 0.5 μmole of NADPH in 3 ml (77). D-amino acid oxidase will be estimated by measuring O_2 consumption from D-alanine in a reaction mixture containing 100 μmoles and pyrophosphate buffer, pH 8.3, 0.5 μg catalase,

10 mμmoles FAD and 60 μmoles D-alanine (78). L-amino acid oxidase will be estimated by measuring O_2 consumption in 0.2 M tris buffer at pH 7.2 containing 0.1 M KCl with 0.1 M l-leucine as substrate (79).

Production of H_2O_2 by intact phagocytes will be determined by an indirect procedure by the oxidation of ^{14}C-formate (80). Direct fluorometric assay for H_2O_2 will also be carried out in cell dialysates by a procedure developed in our laboratory (81). Peroxidase activity will be measured by three different procedures. First, will be the conventional guaiacol oxidase activity by the method of Chance and Mahely which is optimum at pH 7.0 (82). The second procedure will be the decarboxylation of alanine-1-^{14}C catalyzed by peroxidase at pH 5.5 in presence of Cl^- (83,84). Finally, peroxidase will also be assayed by the catalytic iodination of bacteria by the method of Klebanoff (85). Catalase will be assayed by the perborate method of Feinstein (86).

Lysosomal hydrolytic enzymes will be assayed by conventional techniques. Acid and alkaline phosphatases will be assayed with p-nitrophenyl phosphate as substrate with citrate buffer (pH 4.8) and glycyl-glycine buffer (pH 10.4) respectively. Cathespin will be estimated at pH 3.8 by the method of Adams and Smith (87). Nucleotidase will be assayed by the method of Swenseid et al (88) with adenosine-5 phosphate as substrate. Ribonuclease and deoxyribonuclease will be estimated by the procedure of Folette et al (90). Lysozyme will be assayed by the method of Shngar (91).

(5). Phagocytic and bactericidal studies: Phagocytosis will be measured by incubating viable or heat killed bacteria with the phagocytes (50:1) at 37°C for 30 minutes. Smears from the incubation mixture will be stained by May-Greenwald-Giemsa method. Both the number of phagocytes containing bacteria and the number of bacteria per active phagocyte will be counted to estimate the percent phagocytosis and phagocytic efficiency.

Bactericidal activity studies will be carried out using organisms which include pathogenic clinical isolates, those with pathogenecity enhanced by animal passage and laboratory strains from St. Margaret's Hospital stock culture collection. Logarithmic phase cultures of bacteria will be used. The ratio of particles to phagocytes will vary with the experiment. A typical experiment will contain at least two tubes, one being the bacterial control, the other containing both the phagocytes and bacteria. After suitable incubation periods at 37°C, aliquots will be removed from each tube. Those tubes to be evaluated for bactericidal activity will be diluted initially in 5% saponin to lyse the phagocytes. Subsequent dilutions will be in 0.9% NaCl. Aliquots of these dilutions will be plated out in trypticase soy agar using a semi-micro pour plate procedure. These plates will be incubated at 37°C and colonies will be counted by conventional methods.

Peroxidase containing subcellular fractions will also be assayed for bactericidal activity as described for the intact cells. These experiments will be carried out in the presence of a H_2O_2 producing system (glucose-glucose oxidase) and either Cl^- or I^- as halide, at pH 5.5.

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10. Space and facilities available:

The complete facilities of St. Margaret's Hospital will be available for this study. These facilities include:

1. A suite for tissue culture equipped with a walk-in incubator and an explant room under positive pressure. Supporting equipment for this laboratory includes: A Reichert time lapse cinema-micro-photography apparatus, dissection microscope, microscope with phase contrast and inverted microscope, drying ovens, autocalve, refrigerator and deep freeze.

2. A virology laboratory includes a Spinco Model L ultracentrifuge LKB immunoelectrophoresis and immunodiffusion analysis equipment, hood with ultra-violet lamp, pH meter, micromanipulator, refrigerators and freezers.

3. Biochemical facilities include two laboratories equipped with a Spinco Model E analytical ultracentrifuge, Nikon microcomparator, refrigerated centri-fuges, International PR2 and Servall KSB-R with attachment for continuous flow centrifugation, pH stat, Gibson model D electrophorator, facilities for paper chromatography, paper electrophoresis and curtain electrophoresis, electric deslater, Beckman DU and DB spectrophotometers with fluorescence attachment, and amino acid analyzer, fraction collectors, two Warburg constant volume respirometers including a refrigerated model, GC-5 steroid analyzer with a Linear Recorder and a disc integrator, radio-chemical facilities including a Tricarb liquid scintillation spectrometer of the 3000 series and other supporting equipment including pH meters, water baths, analytical balances, Buchler continuous flow evaporators, water deionizers, freeze-dry apparatus, all-glass water still, Buchler constant current power supply of 1000 volt capacity and cold room with walk-in freezer.

4. A laboratory housing the RCA-EMU-3 electron microscope is available for this study and is equipped with dark room for film development and a separate laboratory for the preparation of specimens. A Porter-Blum microtome is available for ultrathin sections along with other supporting equipment.

5. Tissue processing laboratory equipment with routine and experimental histology and histochemistry. The equipment in this laboratory consists of an Autotechnicon, paraffin ovens, microscopes, a cryostat, microtome for frozen section, rotary microtomes, frozen section microscope and deep freeze.

6. Clinical laboratories including blood bank, hematology, bacteriology, biochemistry, urinalysis, endocrinology and immunology sections will be completely available to us for this project.

7. Animal rooms completely air conditioned and equipped to handle infectious and non-infectious experiments, an associated experimental surgery room and a room housing an Andrex Model 3001, 280 kVp x-ray apparatus.

8. An autopsy room with all facilities necessary for teaching and practice.

9. A conference room furnished with projection apparatus for tissue and graphic slides, screen, etc. is available.

10. A larger room equipped with projection apparatus is available for meetings and seminars.

In addition, the facilities required to obtain and prepare patient specimens will be available at the Veterans Administration and Boston City Hospitals. Also, Dr. Joseph Vitale's research laboratories at Boston City Hospital will be utilized as necessary.

11. Additional facilities required:

None.

12. Biographical sketches of investigator(s) and other professional personnel:

Please see curriculum vitaes for A.J. Sbarra, R.J. Selvaraj and J.J. Vitale.

13. Publications:

Please see enclosed reprints.

14. First year budget

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
A.J. Sbarra, Principal Investigator	15	-
J. Vitale, Nutritionist	5	-
R.J. Selvaraj, Biochemist	100	
To be recruited, Res. Tech.	100	
To be recruited, Res. Tech.	100	
Secretary, lab aide	50	
Technical		

Sub-Total for A — R —

B. Consumable supplies (by major categories)

Chemicals, radiochemicals	3,000
Biologicals	2,000
Glassware	1,000

Sub-Total for B 6,000

C. Other expenses (itemize)

Publication costs, travel to attend scientific meetings, maintenance of existing equipment, transporation of samples.

Sub-Total for C 3,000

Running Total of A + B + C 54,000

D. Permanent equipment (itemize)

Oxygraph with recorder	3,000

Sub-Total for D 3,000

E. Indirect costs (15% of A+B+C) E 8,100

Total request 65,100

15 Estimated future requirements

	Salaries	Consumable Suppl	Other Expenses	Permanent Equip	Indirect Costs	Total
Year 2	R	6,600	3,300	-	8,910	68,330
Year 3		7,260	3,630	-	10,301	75,641

xx 19. .

16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
The effect of x-irradiation on the biochemical changes of mammalian cells in the absence and presence of particulate material	AEC AT(11-1) 3517	28,000	August 7, 1972- August 6, 1973

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Metabolism of neoplastic cells during phagocytosis	NIH CA 08317	59,560	September 1, 1973- August 31, 1974

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Anthony J. Sbarra, Ph.D.

Signature [signature] Date 5/30/73

Telephone 617 (Area Code) 436-8600 (Number) 237 (Extension)

Checks payable to

t. Margaret's Hospital

Mailing address for checks

90 Cushing Avenue

Boston, Massachusetts 02125

Responsible officer of institution

Typed Name Sister Mary Bernadette Doyle

Title Administrator, St. Margaret's Hospital

Signature [signature] Date 5/30/73

Telephone 617 (Area Code) 436-8600 (Number) 202 (Extension)

10035398 61

CURRICULUM VITAE

NAME: Anthony J. Sbarra

ADDRESS: REDACTED

BIRTHPLACE: REDACTED

BIRTHDATE: REDACTED

MARITAL STATUS: REDACTED

EDUCATION:

School	Degree	Date	Major
Siena College	B.S.	REDACTED	Biology and Chemistry
University of Kentucky	M.S.		Bacteriology
University of Tennessee	Ph.D.		Bacteriology

SOCIETIES:

REDACTED

RESEARCH INTERESTS:

Biological and biochemical aspects of host-parasite interactions.

POSITIONS HELD:

Associate Biologist, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1953-1956.

Lecturer in Bacteriology, Department of Bacteriology, University of Tennessee, 1954-1955.

Research Fellow, Research Associate, and Instructor in Bacteriology and Immunology, Harvard Medical School, Boston, Massachusetts, 1956-1961.

Associate Director, Department of Pathology and Medical Research, St. Margaret's Hospital, Boston, Massachusetts, 1959-

Assistant Professor of Bacteriology, Tufts University School of Medicine, Boston, Massachusetts, 1959-1963.

Assistant Professor, Associate Professor and Professor of Obstetrics and Gynecology (Microbiology), Tufts University School of Medicine, Boston, 1963-

Editor, Biochemistry Section, Journal of the Reticuloendothelial Society, 1966-

Secretary, Reticuloendothelial Society, 1970.

President, Boston Bacteriologists Club, 1970.

Vice-president, Reticuloendothelial Society, 1971.

President, Reticuloendothelial Society, 1972.

Editoral Board, Journal of Infection and Immunity, 1973.

Councilor, Reticuloendothelial Society, 1973.

PUBLICATIONS

1. Sbarra, A.J. and Hardin, M.M. Attempts to develop strains of Lactobacillus arabinosus and Lactobacillus casei independent of certain growth factors. J. Bact., 61, 99, 1951.

2. Sbarra, A.J. and Hardin, M.M. Attempts to develop strains of Lactobacillus arabinosus 17-5 ATCC 8014 and Lactobacillus casei ATCC 7649 independent of certain growth factors. Masters Thesis, University of Kentucky, 1951.

3. Sbarra, A.J., Woodward, J.M. and Holtman, D.F. A comparison of the free amino acid levels in the blood of rats before and after infection with Bacterium tularense. Bact. Proc., p. 76, 1952.

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11. Sbarra, A.J. and Woodward, J.M. The host-parasite relationship of Tularemia. II. The clinical biochemistry of blood and urine of normal and infected rats. J. Bact., 69, 365, 1955.

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13. Konno, K., Kurzmann, R., Bird, K. and Sbarra, A.J. Differentiation of human tubercle bacilli from atypical acid-fast bacilli. I. Niacin production of human tubercle bacilli and atypical acid-fast bacilli. Am. Rev. Tuberc., 77, 675, 1968.

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15. Sbarra, A.J., Konno, K., Kurzmann, R. and Bird, K. Niacin test for the identification of human tubercle bacilli. Natl. Tuberc. Assoc. Proc., Philadelphia, Penna., p. 68, 1958.

16. Sbarra, A.J. and Karnovsky, M.L. Leukocyte metabolism associated with phagocytosis. Bact. Proc., p. 93, 1958.

17. Karnovsky, M.L. and Sbarra, A.J. Metabolic changes in leukocytes during phagocytosis studied with C^{14}. 2nd Internatl. Conf. on Peaceful Use of Atomic Energy, 24, 82, 1958.

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EDUCATION:

School	Degree	Date	Major
Madras University	B.Sc.	REDACTED	Chemistry
Nagpur University	M.Sc.		Biochemistry
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SOCITIES:

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RESEARCH INTEREST:

Biochemistry of host-parasite relationships

POSITIONS HELD:

Research Assistant, ICMR, Nagpur, India, 1957-1960.

Research Assistant, McGill University, Canada, 1960-62.

Research Associate, Tufts University School of Medicine, Boston, Mass., 1963-65.

Senior Biochemist, Department of Pathology and Medical Research, St. Margaret's Hospital, Boston, Mass., 1965-67.

Assistant Professor of Obstetrics and Gynecology (Biochemistry), Tufts University School of Medicine, Boston, Mass., 1965-67.

Scientific Pool Officer, CSIR, Lucknow, India, 1967-68.

Research Officer, NIN, Hyderabad, India, 1968-69.

Senior Research Officer, NIN, Hyderabad, India, 1969-72.

Senior Biochemist, Department of Pathology and Medical Research, St. Margaret's Hospital, Boston, Mass., 1972-

Assistant Professor of Obstetrics and Gynecology (Biochemistry), Tufts University School of Medicine, Boston, Mass., 1972-

PUBLICATIONS

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EDUCATION:

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New York Univ. Medical School	M.S.		Physiology
Harvard School of Public Health	Sc.D.		Nutrition, Biochemistry
Universidad de Antioquid (Colombia)	M.D.		

SOCITIES:

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RESEARCH INTEREST:

Nutrition as dealing with malnutrition and alcoholism and folate and vitamine deficiencies.

POSITIONS HELD:

Toxicologist, Massachusetts Department of Public Safety, 1949.

Research Assistant, Mallory Institute of Pathology, Boston, City Hospita, 1951-60.

Research Associate in Nutrition, Harvard School of Public Health, 1951-61.

Assistant Professor of Nutrition, Visting Professor of Nutrition, School of Medicine, Universidad del Valle, Cali, Colombia, 1960-62.

Scientific Director, Cali-Harvard Nutrition Project, Universidad del Valle, Cali, Colombia, 1960-62.

Co-director, Tufts Antioquia Collaborative Nutrition Program, 1963-

Co-scientific Director, Medellin, Colombia-Harvard Nutrition Cooperative Program, 1964-66.

Professor of Nutrition, College of Agriculture, University of Wisconsin, 1966.

Research Associate, School of Medicine, University of Wisconsin, 1967.

Senior Pathologist, Research, Mallory Institute of Pathology, Boston City Hospital, 1967.

Professor of Nutrition, Department of Preventive Medicine and Pathology and Director of Nutrition Programs, Tufts University School of Medicine, Boston, Mass., 1967-1972.

Consultant in Nutrition, St. Margaret's Hospital, Boston, Mass., 1969-

Professor of Pathology and Community Medicine, Boston University School of Medicine, Boston, Mass., 1972-

SELECTED PUBLICATIONS:

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